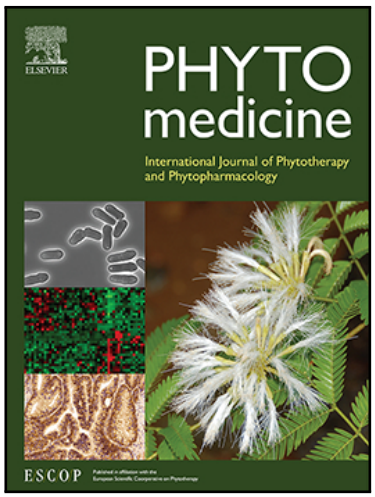
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



A review on computational approaches that support the researches on Traditional Chinese Medicines (TCM) against COVID-19

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A review on computational approaches that support the researches on Traditional Chinese Medicines (TCM) against COVID-19

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Abstract

Background: COVID-19 highly caused contagious infections and massive deaths worldwide as well as unprecedentedly disrupting global economies and societies, and the urgent development of new antiviral medications are required. Medicinal herbs are promising resources for the discovery of prophylactic candidate against COVID-19. Considerable amounts of experimental efforts have been made on vaccines and direct-acting antiviral agents (DAAs), but neither of them was fast and fully developed.

Purpose: This study examined the computational approaches that have played a significant role in drug discovery and development against COVID-19, and these computational methods and tools will be helpful for the discovery of lead compounds from phytochemicals and understanding the molecular mechanism of action of TCM in the prevention and control of the other diseases.

Methods: A search conducting in scientific databases (PubMed, Science Direct, ResearchGate, Google Scholar, and Web of Science) found a total of 2172 articles, which were retrieved via web interface of the following websites. After applying some inclusion and exclusion criteria and full-text screening, only 299 articles were collected as eligible articles.

Results: In this review, we highlight three main categories of computational approaches including structure-based, knowledge-mining (artificial intelligence) and network-based approaches. The most commonly used database, molecular docking tool, and MD simulation software include TCMIP, AutoDock Vina, and GROMACS respectively. Network-based approaches were mainly provided to help readers understanding the complex mechanisms of multiple TCM ingredients, targets, diseases, and networks.

Conclusion: Computational approaches have been broadly applied to the research of phytochemicals and TCM against COVID-19, and played a significant role in drug discovery and development in terms of the financial and time saving.

Keywords: Computational approaches; Traditional Chinese Medicine (TCM); Structure-based approach; Knowledge-mining; Network-based approach

Introduction

COVID-19, the disease caused by the novel coronavirus SARS-CoV-2, caused a global emergency shortly since the late December 2019 (Chitsike and Duerksen-Hughes, 2021; Hu et al., 2021a). As vaccines for COVID-19 have been developed and tested for their efficacy and long-term adverse effects, the latest emerging COVID-19 variant named Omicron may cause the existing vaccines to be less effective due to its heavily mutated species. Moreover, there is no guaranteed for all vaccinated people to be totally protected, so both direct-acting antivirals (DAAs) and vaccines are developed to restrain the spreading of COVID-19. The provided outcomes have not reached satisfaction, and the urgent development of new antiviral medications are required.

Computational approaches are effective strategies in the process of drug discovery and development, and computational methods and tools have grown exponentially in recent decades with the dramatic increase in the availability of computational resources (Tiwari and Singh, 2022). Much of the research effort has focused on the drug discovery against COVID-19 by exclusively computational or computer-aided experimental method, and a commercially available drug named PF-07321332 has been designed and optimized as an orally bioavailable SARS-CoV-2 main protease inhibitor (Owen Dafydd et al., 2021). Medicinal herbs are promising resources for drug discovery because of its favorable efficacy and acceptable toxicity, which can become prophylactic candidate against COVID-19 (Huang et al., 2020; Li et al., 2022a). Recent studies showed that some phytochemicals have been developed as the potential anti-COVID-19 drugs by the computer-aided experimental method (Bharadwaj et al., 2021; Gopinath et al., 2020; Huang et al., 2020; Pamuru et al., 2020; Verma et al., 2020).

Traditional Chinese medicine (TCM) has a long history for over thousands of years of accumulated clinical evidence and pharmacological studies (Gao et al., 2019), and exerts an important role in the prevention and treatment of the COVID-19 caused by SARS-CoV-2 (Lyu et al., 2021; Yang et al., 2020; Zhao et al., 2021d). TCM preparations include extracts from a single source of plants, animals, minerals and their preparations and preparation of TCM formulas. Multicomponent therapeutic formulae are the most important and are most commonly used in TCM for clinical applications. However, the formulae sometimes are very complex which makes it mandatory to use systematic research supported by computational methods to elucidate their mechanisms of action.

In the manuscript, the computational approaches employed in the research of TCM against COVID-19 have been reviewed, and scientific literature with valid experiment and comprehensive studies combining computational investigation will be included in this review until 31st January 2022. The general procedure of computational approaches had been summarized in the Figure 1.

Materials and methods

A systematic review has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and followed the inclusion of relevant studies. The literature search was conducted in the databases: PubMed, Science Direct,

ResearchGate, Google Scholar, and Web of Science for published articles. The keyword 'COVID-19' was paired with 'Traditional Chinese medicine', 'traditional herb', 'natural products', 'active components', 'in silico, 'computational approaches', 'ADMET', 'structure-based', 'molecular docking', 'molecular dynamic simulation', 'ligand-based', 'QSAR', 'pharmacophore', 'generative neural network model', 'chemical cartography', 'chemography approaches', 'knowledge mining', 'artificial intelligence', 'machine learning methods', 'deep learning approaches', 'computer-aided drug design', 'system pharmacology', and 'network pharmacology' to obtain published records until 31st January 2022. Boolean search strategies were used on these keywords without any language restrictions. Data inclusion criteria included (a) the focus of this study is on COVID-19 pandemic disease, and (b) the articles about natural products and/or TCM derivatives conducting *in silico* with experimental validation were included. Exclusion criteria included (a) any data duplication, titles, or content that did not meet the inclusion criteria, (b) reports on antiviral activities of natural products or their derivatives against other diseases, and (c) studies that involved synthetically conventional chemicals, which were not originated from natural sources.

A search conducted in scientific databases (PubMed, Science Direct, ResearchGate, Google Scholar, and Web of Science) found a total of 2172 articles, which were retrieved via web interface of the following websites. After applying some inclusion and exclusion criteria and full-text screening, only 299 articles were collected as eligible articles and displayed in pie charts. All of the extracted information was thoroughly checked by all authors to reach an agreement.

Databases and research resources that support research on TCM against COVID-19

Over the past decades, TCM has promoted its system biology and various data integration in order to modernize and internationalize its concept (Xu et al., 2021a). Several databases have been developed, such as TCMIP (www.tcmip.cn), BATMAN-TCM (http://bionet.ncpsb.org.cn/batman-tcm/), ETCM (www.tcmip.cn/ETCM), SymMap (www.symmap.org), TCMID (http://bidd.group/TCMID/), TCMATCOV (http://tcmatcov.bbtcml.com/), and TCM database@Taiwan (tcm.cmu.edu.tw), etc. Keywords "Traditional Chinese Medicine" and "COVID-19" were paired with each database and found a total of 105 cited databases. These data were screened, and pie chart in Figure 2 was illustrated. The most popular database is TCMSP, which constitutes 44% among all that support research on TCM against COVID-19. TCMIP (11%), BATMAN-TCM (9%), ETCM (9%), SymMap (7%), TCMID (6%), TCMATCOV (5%), TCM database@Taiwan (5%), and other databases (4%) are also applied in the research of TCM against COVID-19.

The results shows that TCMIP (Integrative pharmacology-based traditional Chinese medicine) is the most popular database, which was introduced to solve the aforementioned issues and focus on chemical profiles as well as ADME/PK at first (Xu et al., 2021a).

Structure-based approaches

Structure-based drug discovery (SBDD) methods have been used in numerous pharmaceutical industries and by medicinal chemists to assess binding energy between protein and ligand interactions as well as conformational changes of the receptor during in complex with

a ligand (Kalyaanamoorthy and Chen, 2011). Structure-based approaches usually includes the target structure-based approach and ligand structure-based approach, which will be discussed in the next section of this review.

Target structure-based approach

Target structure-based approach involves target protein structure analysis, molecular docking, and molecular dynamics (MD) simulations. These help researchers to understand disease at a molecular level, specifically identify lead molecules and their optimization in a fast pace (Lionta et al., 2014). Essential steps of SARS-CoV-2 replication cycle have been investigated mainly on S protein, ACE2, TMPRSS2, Mpro, PLpro, RdRp, and other non-structural proteins as described in the previous viral targeted discovery section. The majority of virtual docking programs and databases are used to repurpose potential approved, preclinical, experimental drugs, and natural products. The commonly used docking tools are AutoDock, AutoDock Vina, GOLD, CDOCKER, FlexX, Surflex, G, DOCK6, and SwissDock (Gurung et al., 2021). Following the results of molecular docking, free energy perturbations and binding models are intensively determined using MD software packages including GROMACS, AMBER, CHARM, NAMD, Desmond, Tinker, LAMMPS, and DL_POLY (Gurung et al., 2021). The main objectives of using these tools are to find effective therapeutics for those who are seriously infected by SARS-CoV-2. Target structure-based approach will be further discussed.

Potential targets against COVID-19

SARS-CoV-2 genome consists of nearly 30,000 RNA bases and 29 encoded proteins functioning as host invasion and vital replication. Therefore, successfully inhibiting these target proteins can result in therapeutic actions. The genetic variability of 58 coronaviruses have been assessed in order to determine broad spectrum antivirals (Yazdani et al., 2021). A public web portal named SARS-CoV-2 pocketome was established for displaying 3D structures of 15 SARS-CoV-2 proteins, and 19 putative drug binding sites were mapped on these structures. Scientists can analyze their binding sites of interest for future SBDD efforts. CADD targeting key coronaviral proteins will be summarized with tools using computational modeling.

Three main functional categories of viral proteins include attachment and penetration into host cells, viral replication and transcription, and suppression of the host immune response. To better understand the replicative and host invasive mechanisms of SARS-CoV-2, structure-based drug discovery plays a significant role in rapid determination of many viral protein structures. Several highlighted *in silico* studies covers major targets against COVID-19, which was illustrated in Figure 3.

Docking tools

Molecular docking is popular for identification of potential drug candidates or ingredients in TCM prescriptions. Keywords “Traditional Chinese Medicine” and “COVID-19” were paired and found a total number of 114 cited docking tools listed in Table 1. These data were screened, and pie chart in Figure 4 was illustrated. The most popular docking tool is AutoDock Vina, which constitutes 38% among all that support research on TCM against COVID-19. GLIDE

(18%), AutoDock (15%), MOE (10%), SwissDock (5%), GOLD (2%), COVID-19 Docking Server (2%), and other docking tools (10%) are also applied in the research of TCM against COVID-19.

The results shows that AutoDock Vina is the most popular docking tool in the target structure-based approach. AutoDock Vina is an open-source molecular docking program, which can virtually pre-calculate grid maps without any requirements on choosing atom types because it calculates the grids internally and instantly for the atom types that are needed (Trott and Olson, 2010).

Molecular dynamics simulations

MD simulations can obtain comprehensive information about drug target dynamics and potential ligand interactions. These are several most commonly used softwares for MD calculations: AMBER (Case et al., 2005; Song et al., 2019), YASARA (Land and Humble, 2018), GROMACS (Groningen MAchine for Chemical Simulation) (Selvaraj et al., 2021b), VMD (Visual Molecular Dynamics) (Umesh et al., 2021), CHARMM (Chemistry at Harvard molecular mechanics) (Brooks et al., 2009), NAMD (Gyebi et al., 2020; Lee et al., 2016), Desmond (Patel et al., 2021), and Tinker (Sawant et al., 2021). Keywords "Traditional Chinese Medicine" and "COVID-19" were paired and found a total number of 80 cited MD simulation software. These data were screened, and pie chart in Figure 5 was illustrated. The most popular MD simulation software is GROMACS, which constitutes 22% among all that support research on TCM against COVID-19. Desmond (20%), AMBER (16%), CHARMM (14%), YASARA (9%), VMD (6%), NAMD (4%), Tinker (1%), and other MD simulation software (8%) are also applied in the research of TCM against COVID-19.

The results shows that GROMACS is the most popular MD software in supporting with the research of TCM against COVID-19 facilitate the potential drug discovery and target identification

Examples of active compounds derived from TCM by structure-based approaches

We briefly review some hit natural products that have been further investigated for experimental validation using structure-based approaches. Several natural compounds have been evaluated for their activity against SARS-CoV-2 S protein, $3CL^{pro}$ and PL^{pro} in virus-infected cells as shown in Table 3, 4, and 5.

ACE2 (S protein) inhibitors:

Viral attachment and entry are of particular interest therapeutic targets in the life cycle of viruses. SARS-CoV-2 use the receptor-binding domain (RBD) of its glycosylated S protein to bind to human angiotensin converting enzyme 2 (hACE2) and initiate membrane fusion and virus entry. Hence, the inhibitor of the RBD–hACE2 protein–protein interaction (PPI) can disrupt infection efficiency (Bojadzic et al., 2021). Some natural compounds isolated from natural extracts are listed in Table 3 as the ACE2 (S protein) protein inhibitors.

Here is a detailed example by structure-based approaches: Elebeedy *et al*. reported four major active compounds against SARS-CoV-2 S protein, which are tanshinone IIA and salvianolic acid B from TCM herb *Salvia miltiorrhiza* and carnosic acid and rosmarinic acid from *Rosmarinus officinaliss* (Elebeedy et al., 2021). Molecular docking and MD simulation studies have been performed on all four compounds and showed promising anti-SARS-CoV-2 binding affinities. Therefore, to validate the computational model, the activity of these compounds was further conducted *in vitro* using plaque reduction assay and MTT assay on Vero E6 cells for IC_{50} and CC_{50} values respectively. The promising activity of Tanshinone IIA, carnosic acid, rosmarinic acid, and salvianolic acid B ranged as following from lowest to highest with IC_{50} of 4.08, 15.37, 25.47, and 58.29 ng/μL. All compounds demonstrated no significant cytotoxic effects on Vero E6 cells.

Chymotrypsin-like ($3CL^{pro}$) inhibitors:

SARS-CoV-2 $3CL^{pro}$ (M^{pro}) is well known to be ideal target for treating COVID-19, and several natural products from different sources including TCM herbs and formulas have potential antiviral activities on the main protease. Some natural compounds isolated from natural extracts are listed in Table 4 as the M^{pro} inhibitors.

One study has screened 1920 natural products and identified two anti-SARS-CoV-2 compounds, namely ginkgolic acid and anacardic acid (Chen et al., 2021c). Both demonstrated similar IC_{50} values of 1.79 and 2.07 μM respectively. No significant cytotoxicity effects were observed at 20 μM for ginkgolic acid and anacardic acid. Simultaneously, these two hits can block SARS-CoV-2 replication at non-toxic concentration of 15 μM in a viral plaque reduction assay. Epigallocatechin gallate (EGCG), an active ingredient in TCM commonly known as green tea was a promising inhibitor of SARS-CoV-2 M^{pro} (Du et al., 2021).

Papain-like protease (PL^{pro}) inhibitors:

Papain-like protease (the phosphatase domain of nsp3) is believed to interfere with the immune response by acting as a ADP-ribose phosphatase to remove ADP-ribose from host proteins and RNAs, and then is the therapeutic target against COVID-19(Freitas et al., 2020; Klemm et al., 2020; Shin et al., 2020). Some natural compounds isolated from natural extracts are listed in Table 5 as the PL^{pro} inhibitors.

One study further investigated numerous natural PL^{pro} inhibitors from the phytochemical library named national compound library of traditional Chinese medicines (NCLTCMs), which contained more than 9000 TCM compound derivatives and proved with valid experiment of fluorogenic enzymatic and Pro-ISG15 cleavage assays (Li et al., 2022b). The total of nine natural hits, namely amentoflavone, ginkgetin, isoginkgetin, sciadopitysin, morelloflavone, podocarpusglavone, hinokiflavone, cryptomerin B, and 4'-O-methylochnaflavone demonstrated effective PL^{pro} inhibitors with anti-proteolytic activity and IC_{50} ranging from 9.5 to 43.2 μM in the enzymatic assay. Moreover, this study was reported for the first time that 4'-O-methylochnaflavone exhibited promising inhibitory effects on both proteolytic and deISGylation activities of SARS-CoV-2 PL^{pro}. This natural product remarkably suppressed PL^{pro}-induced deISGylation at decreased concentration of 2.5 μM with 60.7% inhibition rates. Pitsillou *et al.*

performed enzymatic inhibition assay of natural hits namely hypericin, rutin and cyanidin-3-O-glucoside, which are small molecules SARS-CoV-2 PL^{pro} inhibitors at 100 micromolar range (Pitsillou et al., 2021). These natural compounds were screened from OliveNet™ library, subjected to molecular docking using the selective PL^{pro} inhibitor, GRL-0617, as control, and further implemented MD simulation at 100 μs prior to *in vitro* evaluation. In another study, cryptotanshinone and tanshinone I, two active components in TCM herb named *Salvia miltiorrhiza*, were identified as top PL^{pro} inhibitors with IC_{50} = 5.63 and 2.21 μmol/L respectively (Zhao et al., 2021b). Both compounds were performed using qRT-PCR analysis, immunofluorescence microscopy, plaque-reduction, and cytotoxicity assays using a clinical isolate of SARS-CoV-2 (nCoV-2019BetaCoV/Wuhan/ WIV04/2019) infected Vero E6 cells. EC_{50} was of 0.70 and 2.26 μmol/L for cryptotanshinone and tanshinone I respectively for a plaque-reduction assay. This means that the penetration of viral cellular membrane by these two hits created access to the PLpro target.

Ligand structure-based approaches

In this section, the application of traditional ligand-based methods and knowledge mining approaches will be discussed. This can exploit and lead to the experimental drug discovery for COVID-19. We highlight the utility of some recent innovative techniques such as Generative Topographic Mapping (GTM) and deep learning (DL) for the discovery of novel DAA agents.

Chemical cartography or chemography approaches

Chemical cartography or chemography approaches, allows visual analysis of an ensemble of chemical structures encoding vectors of molecular descriptors, which can project extremely complex data onto a 2D chemical space map (Gaspar et al., 2015). This method utilizes the neighborhood behavior principle, which suggests that close-proximity compounds have similar chemical properties, so chemical space maps can relate to structural-activity relationship (SAR) studies. Joshi *et al.* conceptualized the key druggable parameters of chemical space and analyzed molecular similarity on already identified phytochemicals in COVID-19 (Joshi et al., 2021). Chemical space exploration using key parameters including MW, TPSA, number of rotational bonds (nROTB), hydrogen bond donors (nHBDon) and acceptors (nHBAcc), and partition coefficient (AlogP) using Platform for Unified Molecular Analysis (PUMA) online server (Gonzalez-Medina and Medina-Franco, 2017). These parameters were used to compare potential hit compounds from *in silico*-based studies from natural sources against Covid-19, FDA approved drugs from natural products, and with FDA approved anti-infectives. A strong correlation of identified phytochemicals was observed and was further subjected to molecular docking and MD simulation.

Generative Topographic Mapping (GTM) is one of the most commonly used chemical space mapping (chemography) methods. It is a non-linear grid-based method, which can be used for visualizing data, modeling structural activity, and evaluating database comparison. The GTM algorithm has 2D smooth surface called manifold fitted into a high-dimensional descriptor space and subsequently projected molecules on 2D latent space superposed with a square grid of nodes (Lin et al., 2020a). The results of biological tests can be involved with a map through activity or

classification landscapes, which can visualize the specific sites surrounded by molecules with a provided activity along with proximity-based classification of untested compounds (Bocci et al., 2020). In the past, there was no available experimental data for drug discovery against SARS-CoV-2, so information was mainly associated with related pathogens. Moreover, GTM was implemented for visualizing the interactive chemical space of natural product databases including ChemGPS-NP, COCONUT, D-Peptide Builder, and an intuitive online tool NP Navigator (Medina-Franco et al., 2021; Sorokina et al., 2021; Zabolotna et al., 2021). These are open-source and easily accessible tools and websites to calculate molecular descriptors and interpret chemical space notion of small molecules derived from natural product. Zabolotna *et al.* introduced the Natural Product Universal map (NP-Umap) and obtained density landscape of natural products from COCONUT to support the investigation of natural product chemical space (Zabolotna et al., 2021). The ISIDA descriptors have also been used to explore the chemical space of natural product. MinHashed Atom Pair fingerprint with diameter of four bonds (MAP4) was reported as a molecular fingerprint with good performance in similarity searching and chemical space visualization for different molecular sizes, which were analyzed in Natural Products Atlas (NPAtlas) containing microbial origins (Capecchi et al., 2020; Capecchi and Reymond, 2020). These could be great ideas for conducting experimental research using natural product databases, molecular descriptors and fingerprints, chemical space navigation of natural product against COVID-19.

Generative neural network models

Different from virtual screening of available chemical libraries, constructing *de novo* molecule provides access to a virtually infinite chemical space and offers innovative molecular architecture with desired properties (Yang et al., 2019). Recently, the use of generative artificial intelligence to develop drug-like chemical compounds with desirable pharmacological effects supports drug discovery of DAA agents (Schneider and Clark, 2019). Recent generative approaches usually construct on deep neural networks (DNNs), which aims to model the underlying distribution of a given set of molecules and by sampling from the modelled distribution to construct novel chemical entities (Foster, 2019). The application of recurrent neural networks (RNNs) with long short-term memory (LSTM), variational autoencoders, generative adversarial networks (GANs), graph neural networks (GNNs), and other network architectures have been studied (Grisoni and Schneider, 2019; Lin et al., 2020b; Pogány et al., 2018; Sattarov et al., 2019). These approaches are trained using ML algorithms to understand the meaning of text and language analytics. For the purpose of molecular design, the training molecules are represented in form of string notations as simplified molecular-input line-entry systems (SMILES strings). This generative DL model is important because internal representations of SMILES are automatically derived without relying on human-engineered molecular descriptors that require one's prediction of physicochemical properties. The generative model captures the syntax corresponding to valid training molecules and renders new SMILES-encoded molecules of interest, which can also lead to discovery of novel compounds with desired bioactivities (Merk et al., 2018). Bung *et al*. employed deep neural network-based generative and predictive models for *de novo* design of small molecules with SARS-CoV-2 $3CL^{pro}$ inhibitory effects (Bung et al., 2021). Transfer learning followed by reinforcement

learning aided the design of protease-specific inhibitors with optimized new chemical entities (NCEs) properties. The SymMap database of TCM was used to compare the potent NCEs by generative model that potentially targeted $3CL^{pro}$ (Wu et al., 2019). 33 NCEs were selected for the identification of pharmacokinetic and toxicity properties using SwissADME, ToxTree, and pkCSM (Bung et al., 2021). Two NCEs shared similar results of Tanimoto coefficient of 0.80 to the natural product named aurantiamide. This phytochemical was extracted from *Baphicacanthus cusia*, the TCM herb treating cold, fever, and influenza, and possessed anti-viral properties. The generalized approach was used to rapidly accelerate drug discovery process and tested against SARS-CoV-2 $3CL^{pro}$.

Another study has developed deep learning model using convolutional neural network (CNN) framework for predicting compounds with $3CL^{pro}$ inhibitory activity (Kumari and Subbarao, 2021). 423 unique chemical structures including 80 active and 343 inactive compounds as chemical descriptors were trained into the CNN model. Classification ML approaches including Random Forest, naïve Bayes, decision tree, and support vector machine were also implemented to compare with the CNN model. The results of the test set exhibited an accuracy, sensitivity, specificity, precision, recall, F-measure, and ROC of 0.86, 0.45, 0.96, 0.73, 0.45, 0.55, and 0.71 respectively. The CNN architecture screened 10 hit molecules from phytochemical compounds, 59 hits from NCI divest IV and 14,025 ZINC natural product database as anti-COVID-19 agents.

Examples of active compounds derived from TCM by ligand-based approaches

The examples of active compounds from TCM by structure-based approaches have been previously discussed. Only few studies have been investigated on main TCM components acting against COVID-19 using ligand-based approaches, which will be reviewed in this section. Rahman *et al.* reported a ligand-based pharmacophore approach using the Molecular Operating Environment (MOE) software (Rahman et al., 2020). Approximately 30,927 compounds from NPASS were screened for the pharmacophore features of standard serine protease inhibitor camostate mesylate, which is a trypsin-like protease inhibitor. Subsequently, 2140 compounds were identified from the ligand-based compound screening approach and further subjected to molecular docking against TMPRSS2 to determine potent inhibitors of this target. The authors selected 10 pharmacophoric features including anionic and cationic atoms, H-Bond donor and acceptor, aromatic center, Pi ring center, and a hydrophobic center. Following physicochemical and ADMET prediction, NPC306344 was the hit compound for TMPRSS2. Further investigation on experimental and animal studies is required to develop this anti-COVID-19 drug. Gaudêncio & Pereira proposed five marine natural products, such as Reaxys ID: 7450892, 19384758, 26845562, 10714788, and 10720065 as most promising SARS-CoV-2 M^{pro} inhibitors using quantitative structure-activity relationship (QSAR) classification modeling (Gaudêncio and Pereira, 2020). This CADD ligand-based study consists of two extensive sets of descriptors including six different types of fingerprints with different sizes and 1D&2D descriptors. These molecular descriptors and fingerprints were calculated using PaDEL-Descriptor version 2.21, available on http://www.yapcwsoft.com/dd/padeldescriptor/. Random Forest (RF) machine learning technique was used for constructing classification modeling to evaluate performance of

SARS-CoV-2 activity. The authors highlighted three selected models, which are MACCS model, ExtCDK model, and 1D&2D descriptors. The best MACCS model built with sets of fragment fingerprints include MACCS, Sub, Sub C, and PubChem, and the best ExtCDK model built with sets of circular fingerprints include CDK and CDKExt. For 1D&2D descriptors, Q and MCC parameters were selected. The best model for each training set of ExtCDK fingerprints and 1D&2D descriptors were obtained by using the RF algorithm of the selected 150 fingerprints and descriptors respectively. MACCS model was excluded because descriptors comprise only 166 fingerprints. Probability of being class A (Prob_A) can be used as an additional parameter assigned by the RF algorithm and a predicting criterion (≥0.5). JChem Standardizer tool version 5.7.13.0 was then used to standardize the molecular structures of all data sets by normalizing tautometic and mesomeric groups and removing small disconnected fragments. The pkCSM software was used to predict fifteen selected marine natural products by QSAR model, molecular docking, and ADMET properties. Finally, the top five aforementioned marine natural products were achieved and could be further investigated experimentally. Ghosh et al. reported the development of multiple classification QSAR models including several Monte Carlo optimized-based and structural and physicochemical interpretation (SPCI) analysis with a diverse dataset of 88 compounds with SARS-CoV-2 M^{pro} inhibitory properties (Ghosh et al., 2021). In SPCI analysis study, four machine learning approaches including Gradient boosting classification (GBC), Random Forest (RF), Support Vector Machine (SVM), and *k*-nearest neighbor (*k*NN) are used to perform diverse classification-based QSAR models for identifying and predicting different fragments that contribute for M^{pro} inhibition. These models were further assessed for balanced accuracy, sensitivity, and specificity (Polishchuk et al., 2016). The results of SPCI analysis suggested heterocyclic scaffolds including diazole, furan, and pyridine have a positive contribution, while thiophen, thiazole, and pyrimidine seem to have negative contribution to M^{pro} inhibition (Ghosh et al., 2021). Furthermore, Monte Carlo optimization-based QSAR was implemented to screen some natural product hits from recent publications. SMILES-based descriptors, Graph-based descriptors, and Hybrid descriptors are employed in this study. The statistical characteristics of twenty-one different models from three different splits were obtained from Monte Carlo optimization method, and the model **M21** (SMILES and HSG with $^{1}EC_{k}$) from split-3 was applied for the best model screening. Subsequently, 13 active molecules from natural sources were found as the most potent coronaviral M^{pro} inhibitors. These compounds consist of one lignan, eleven flavonoids, and one pentacyclic triterpenoid. This approach plays a significant role on fragment investigation and QSAR based active compound screening against SARS-CoV-2 M^{pro} enzyme.

Knowledge mining tools

The COVID-19 pandemic results in urgent establishments of open science and FAIR (Findable, Accessible, Interpretable, Reusable) data initiatives to help researchers, institutions, publishers, companies and regulators better understanding the disease and search for effective treatment as soon as possible (Wilkinson et al., 2016). For instance, the Natural Products Atlas, a microbial natural product database with over 20,000 compounds containing structural data references, compound names, source organisms, isolation references, total syntheses, and structural reassignment, has been developed using FAIR principles as a community-supported

resource for known structural characterizations of microorganisms from natural product (Van Santen et al., 2019). Various structured and unstructured COVID-19 data sources have been made publicly available. This highlights the use of accelerated tools for COVID-19 drug discovery from knowledge graph approaches and AI, which will be discussed with examples in the following section (Bullock et al., 2020).

Knowledge graph (KG) is a collection of integrated knowledge resources or correlation between library and data descriptions in a form of mapping graph (LiuQiao and DuanHong, 2016). KG implemented visualization AI technology to illustrate, construct, connect knowledge resources, and display relationships between these carriers. In TCM field, the use of KG analysis could explain complex relationships between therapeutics and prevention of diseases as well as other research fields, which could be an alternative for studying the information on TCM. Several studies have applied KG to the TCM diagnostic and medical treatment (Wang, 2020; Yu et al., 2017; Zhao et al., 2020a). However, in this review, the TCM prescription using COVID-19 KG will be summarized in detail.

FP-Growth algorithm, a modified version of Apriori algorithm, has been developed for analyzing TCM data correlation between natural active constituents in 41 TCM prescriptions with 8 characteristics of medical properties, 10 kinds of medical tastes, and 10 kinds of meridian tropism (Yan et al., 2020). In this study, Neo4j, a high-performance NoSQL graph database, as well as various programming languages, for instances Python, Java, GO, R, etc. were also provided in order to construct COVID-19 KG. Three populations including medical observation, mild general, and COVID-19 infected patients were included in the study with equally distributed number ratio of 1:1:1 to enhance reliable association analysis results. To be more specific, TCM prescriptions for COVID-19 infected patients will be summarized in our review. There are two major modules, which comprises of FP-tree construction by FP-Growth algorithm and the use of Cypher language analysis on the algorithm to map the graph of COVID-19 prescription. The initial step was to establish relationships between tastes, properties, and population and make correlation analysis to produce the graph of "applicable population – properties, tastes, and meridian tropism of Chinese medicinal herbs" (Yan et al., 2020). The results demonstrated that TCM herbs with neutral property, acrid taste, and spleen-invigorating meridians were commonly used in the prescriptions to treat COVID-19 infected patients. The highest proportions of each TCM characteristics type of herbs in COVID-19 prescriptions statistically contributed 39% of warm-natured properties, 41% of acrid tastes, and 24% of stomach meridian tropism. Subsequently, the use of operation instructions, such as MATCH and WHERE in Cypher suggested that core TCM herbs including Radix Glycyrrhizae (Gan Cao), Herba Asari (Xi Xin), Rhizoma Atractylodis (Cang Zhu), and etc. were recommended as well as TCM prescriptions including phlegm-resolving, wind-dispelling, cough/pain/exterior syndrome-relieving, spleen-invigorating, and digestion-aiding medicines for the COVID-19 infected patients. Further investigations on improving KG efficacy are required. For examples, the KG of COVID-19 prescriptions reported here only supported a small number of data, so FP_G algorithm should be applied to enhance FP_tree construction in FP-Growth algorithm for a larger volume of prescription data expansion. The use of knowledge graph approaches for COVID-19

TCM prescriptions could be applied in relevant research scholars and increased the reliability of TCM research content.

Network-based approaches

Network-based approaches is very important for network pharmacology, system pharmacology and integrated pharmacology research on TCM against COVID-19.

Network pharmacology

Network pharmacology comprehensively integrates multitarget drugs and compound-disease pathways in order to comprehend complex biological systems, drugs, and diseases in a network point of view. This results in shifting drug discovery concepts of network theory and systems biology from the concept of one gene, target, and disease to the novel paradigm of multitargeted mechanisms in treatment of complicated diseases, especially COVID-19.

Zhang *et al*. conducted a network pharmacological methodology to explore significant biological mechanisms of Lianhua Qingwen Capsule (LHQWC), which is another TCM formula used for treating respiratory diseases as well as COVID-19 (Zhang et al., 2021a). 263 ingredients of 13 herbs, including *Fructus Forsythiae, Flos Lonicerae Japonicae, Herba Ephedrae, Almond, Radix Isatidis, Fortunes Boss fern Rhizome, Herba Houttuyniae, Herba Pogostemonis, Rheum palmatum, and Glycyrrhiza uralensis Fisch*, were retrieved from TCMSP database while *Rhodiola rosea, Mentha haplocalyx Briq and Gypsum Fibrosum* were retrieved from BATMAN-TCM and TCMID databases (Liu et al., 2016; Xue et al., 2012). 226 compounds excluding duplicated portions from these herbs were selected for further study. To standardize the protein name, UniProtKB was utilized to acquire the official symbols (Consortium, 2015). The gene intersection between active ingredients and COVID-19 was illustrated and visualized using a Venn diagram (Heberle et al., 2015). GeneCards database was used to obtain COVID-19 human related genes (Rebhan et al., 1997), and the STRING database was employed to predict PPI interaction data (Mering et al., 2003). 643 therapeutic genes were collected from GeneCards for COVID-19 and 49 intersected genes were generated. These ingredient-disease co-target genes were further imported into STRING to construct PPI. GO and KEGG pathway enrichment were further carried out using R package to determine biological processes and molecular interactions associated with top 20 selected common genes (Kanehisa and Goto, 2000). Ingredient–target network and ingredient–disease PPI networks were analyzed and constructed using Cytoscape software (Shannon et al., 2003). The ingredient-target network contains 153 nodes (49 targets and 104 compounds) and 299 edges, which represent a biological relationship between two nodes. LHQW-C may exert synergistic pharmacological effects on COVID-19 as suggested by the degree (number of links to nodes) of compounds. For instance, quercetin (degree 38), luteolin (degree 17), wogonin (degree 12), and kaempferol (degree 11) exhibited multiple targets in network regulation. On the other hand, the result revealed PPI network consisted of 46 nodes and 331 edges. Nodes with an average value of degree ≥27, node betweenness ≥0.0009993, and closeness ≥0.618 suggested that the target network of LHQW-C plays significant roles on IL-6, TNF, MAPK1, which were associated with inflammatory responses, oxidative stress reactions, and other biological processes. Finally, the potential mechanism of LHQW-C using an

integrating network pharmacology method suggested that some anti-inflammatory ingredients may inhibit viral replication, suppress cytokine storm, and protect the pulmonary alveolar-capillary barrier in patients with serious COVID-19 illness.

Similarly, Li *et al*. reported the antiviral and anti-inflammatory effects of Maxing Shigan decoction (MXSGD), the key formula for treating pulmonary diseases, using multiple open-source TCM databases, network pharmacology, PPI construction, as well as biological enrichment analysis (Li et al., 2021c). Four TCM herbs in MXSGD formula consist of *E. sinica, S. armeniacae amarum, G. Fibrosum,* and *G. uralensis* have proved to be effective against COVID-19, and Lianhua Qingwen Capsule, Qingfei Paidu decoction, Huashi Baidu formula, and Xuanfei Baidu granule, were all formulated based on MXSGD. Ye *et al.* reported the ingredients of Toujie Quwen Granules were proved to have therapeutic effects on COVID-19 via regulating viral infection, immune and inflammatory related targets and pathways using network pharmacology, molecular docking, and surface plasmon resonance technology (SPR) (Ye et al., 2021). The results of SPR experiments revealed the combination of quercetin and isoquercitrin preferably bound to SARS-CoV-2 S protein while astragaloside IV and rutin selectively bound to ACE-2. He *et al*. identified the therapeutic effect of Xuebijing injection on COVID-19-induced cardiac dysfunction using bioinformatics analysis (He et al., 2021). Xuebijing injection indicated oxidative stress inhibition, atherosclerotic plaque prevention, inflammatory repression and apoptosis by targeting 7 central hub genes including CCL2, CXCL8, FOS, IFNB1, IL-1A, IL-1B, SERPINE1 that have protective mechanism on COVID-19-induced cardiac dysfunction. Lin *et al*. systematically and comprehensively analyzed the active ingredients, targets, and possible mechanisms of Yinqiao powder for treating COVID-19 using drug-ingredient-gene and PPI network construction as well as GO and KEGG pathway analysis (Lin et al., 2021). The active ingredients of Yinqiao powder, such as hesperetin, eriodictyol, luteolin, quercetin, and naringenin have antagonistic effect on the inflammatory storm caused by COVID-19 and may be associated with the regulation of IL-6, MAPK3, TNF, and TP53 targets using network pharmacology. Tao *et al*. proposed the therapeutic mechanism of Shufeng Jiedu Capsule (SFJDC) against SARS-CoV-2 pneumonia using an integrated systemic study of ADME assessment, target fishing, network construction, and functional bioinformatics analyses to understand potential immunomodulatory and anti-inflammatory mechanisms (Tao et al., 2020). Many TCM prescriptions have been investigated using network pharmacology methods due to complicated multiple TCM ingredients, targets, diseases, and mechanisms. Next, discussion part will be mentioned.

System pharmacology

The combination of herbal medicine formula contains over thousands of chemical compounds, and only some parts of them show favorable pharmacokinetics along with potential biological effects (Li et al., 2012). Moreover, possible therapeutic effects of herbal products might result from cooperate actions of the herbal ingredients. This concept screens out the conventional analytical chemistry and pharmacology technologies which attempt to isolate and identify possible pharmacological effects of chemical constituents. Also, the chemical components in multiple TCM herbs or even in one herb are too complex to identify because they

produce various biological targets involving in various pathogenesis. Due to these addressed issues, systems pharmacology has been applied in a biological complex system for screening drug safety, active compounds, predicting the targets, and analyzing the potential ingredient target-disease networks.

A unique system pharmacology platform of Chinese herbal medicines named Traditional Chinese medicine systems pharmacology (TCMSP) was developed for accelerating drug discovery from herbal medicines (Ru et al., 2014). This database covers a large-scale structural data integration with experimentally validated information for all registered herbs in Chinese pharmacopoeia, active compound screening with key ADME-related properties from diverse sources, compound-target and target-disease network construction with applied TCM theory, as well as mechanisms of action and discovery of new drugs. Wang *et al*. systemically reported the pharmacological effects and mechanisms of Jingyin granule containing multiple herbs for treating respiratory system diseases using computational approaches (Wang et al., 2021a). Firstly, the ingredients in Jingyin granule were assessed using TCMSP and Traditional Chinese medicine integrated database (TCMID). These databases were used to search for the identified herbal ingredients with ADME properties, oral bioavailability (OB), and drug likeness (DL). A total of 168 selected druggable ingredients identified in Jingyin granule were screened in TCMSP database with the criteria of OB ≥ 30% and DL ≥ 0.18. Subsequently, 865 potential therapeutic targets of ingredients were identified using SwissTargetPrediction database, and for possible targets of COVID-19, Online Mendelian Inheritance in Man (OMIM), DisGeNET, and GeneCards databases were implemented and identified 88 interacting genes as potential therapeutic targets of Jingyin granule to COVID-19. As a result of using these computational approaches, Jingyin granule could directly target the ACE gene, and ACE protein shared similar domain with ACE2, which had been identified as one of the most important targets for SARS-CoV-2 entry (Wang et al., 2021a). Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were further investigated for these relevant target genes with similar functions using an R package clusterProfiler (Yu et al., 2012). The results of GO and KEGG analysis suggested Jingyin granule could regulate immunoreaction as Flos lonicera and Licorice demonstrated anti-inflammatory activities (Wang et al., 2021a).

Another example of system pharmacology was included in the study of TCM Shenfuhuang Formula (SFHF) in treatment for septic syndrome of COVID-19 (Liu et al., 2020). Data mining was performed and collected 231 ingredients from SFHF, including 92 ingredients of *Rheum palmatum* L. (Da Huang), 74 compounds of *Panax ginseng C.A.Mey* (Hong Shen), and 65 compounds of *Aconitum carmichaeli Debeaux* (Fu Zi) from TCM pharmacology analysis databases, TCMSP and ETCM. Suitable drug candidates were selected when they fulfilled active screening criteria including oral bioavailability (OB) ≥ 30%, Caco-2 permeability (Caco-2) > −0.4, drug-likeness (DL) ≥ 0.18, and half-life (HL) ≥ 4. Only 49 potential SFHF compounds were selected. Weighted ensemble similarity (WES) approach was also utilized to obtain comprehensive drug target information of SFHF. The results of 64 identified targets were predicted for the 49 potential drug compounds. In compound-target analysis network, compounds with most targets (sitosterol, emodin, chrysophanol, and deltoin) as well as proteins

(GSK3β, ESR1, PPARG, PTGS2, AKR1B10, and MAPK14) were determined (Liu et al., 2020). SFHF was further analyzed in PharmGKB, Drugbank, and TTD databases for a target-disease network, and the results suggesting 46 targets were directly involved with immune system as well as nine potential targets on inflammatory disease. KEGG and DAVID databases were subsequently connected potential targets and related signaling pathways. These signaling pathways, such as Toll-like receptor, MAPK, JAK/STAT, PPAR, VEGF, NOD-like receptor and NF-kappa B have a strong relationship with sepsis, infection immunity, inflammatory response, coagulation function, organ damage, immune disorders and other diseases. Furthermore, synergistic effects of three herbal compounds in SFHF were constructed, and the targets of this TCM formula were related with the calcium, MAPK, T cell receptor, and PI3K-AKT signaling pathways. These are main pathological pathways for sepsis. There are more upcoming studies on TCM formulas with system pharmacology approaches and MOA analysis for COVID-19 in the future.

Discussion

COVID-19 pandemic has globally brought researchers to conduct extensive studies in order to comprehend pathological diseases, viral components of protein structure, and viral-host interactome. The current search for potential antiviral inhibitors, such as vaccines seems to be massively time-consuming as well as conventional drugs with undesirable effects in a long term. Hence, the search for accelerated methods, safe, and effective antiviral drugs is required. Computer-aided drug discovery (CADD) approaches play a significant role in simulating drug-target interactions, analyzing potential drug targets, and accurately predicting hit compounds by using bioinformatics databases, docking tools, software, and other computational methods for the optimization of drug design. In the early stage of drug discovery, CADD can save time, financial investment, and economical resources spending on wet lab, and prove chemical safety profile of natural ingredients in TCM. An effective CADD approach was previously utilized to study modern sciences of complex multi-target diseases and mechanisms using TCM formula and/or natural products derived from TCM (Yang, 2013). Moreover, a recent study on CADD, publication resources, and other computational approaches was implemented to discover novel drug candidates against COVID-19 (Muratov et al., 2021). We truly inspired by the concept of these two studies, so we focus on small molecule drugs derived from natural products and Traditional Chinese Medicine (TCM) in treatment of COVID-19 using CADD approaches.

In this review, there are more studies mentioning on databases and research resources, docking tools, and MD simulation software that aid TCM drug discovery against COVID-19. For instances, the identification of natural hit compounds named Gracillin and Proanthocyanidins from traditional medicinal plants were virtually screened using AutoDock Vina and visualized by Discovery Studio Visualizer, and both exhibited the highest binding affinity of 9.2 kcal/mol to $3CL^{pro}$ (PDB ID: 6WNP) (Khanh and Hoa, 2021). Elekofehinti *et al*. reported post-docking analysis by MM/GBSA of the natural hit compound named STOCK1N-98687 from natural products library and confirmed binding stability of the ligand and $3CL^{pro}$ complex (Elekofehinti et al., 2021). STOCK1N-98687 has high GLIDE docking score against SARS-CoV-2 $3CL^{pro}$, induced-fit docking score, and satisfactory calculated binding free energy score with good

predicted inhibitory prowess (pIC50) compared to the experimental drug lopinavir. 50 ns MD simulation was performed using GROMACS software and revealed high stability with low fluctuation of the complex suggesting STOCK1N-98687 as the potential $3CL^{pro}$ inhibitor. Pie charts are illustrated in Figure 2, 4, 5, and the most popular database, docking tool, and MD simulation software on TCM research articles against COVID-19 are TCMSP, AutoDock Vina, and GROMACS respectively. However, this can be further indicated that databases, tools or MD software conducting on TCM research articles against COVID-19 are low in number of publications. Many readers could take this opportunity to exploit and develop their own TCM-related research field against COVID-19 from our review.

We have found more *in vitro* examples of active ingredients on TCM using structure-based approaches while ligand-based approaches will be summarized using *in silico* methods. QSAR classification modeling was constructed using RF machine learning techniques in order to propose five marine natural products (Reaxys ID: 7450892, 19384758, 26845562, 10714788, and 10720065) as top SARS-CoV-2 M^{pro} inhibitors (Gaudêncio and Pereira, 2020). Deep neural networks were employed for generating *de novo* design of small molecules and compared 33 NCEs with TCM phytochemicals in order to determine which compounds are able to inhibit SARS-CoV-2 $3CL^{pro}$ (Bung et al., 2021). In this study, aurantiamide from TCM herb *Baphicacanthus cusia* possessed antiviral properties, and this method can accelerate drug discovery process. For knowledge mining tools, the use of COVID-19 knowledge graph can be applied in TCM prescriptions for diagnostic and medical treatment (Yan et al., 2020). The applications of systems pharmacology focus mainly on a biological system including active ADME screening model, target prediction, and compound target-disease network analysis. For network pharmacology, the integration across multiple drug-target and ingredient-disease pathways totally shifts the paradigm of drug discovery from one gene, target, and pathway to complex network theory, biological systems, and multiple target mechanisms. Many TCM formula have included both systems pharmacology and network pharmacology in their research articles for better understanding of their multiple mechanisms and targets. Different CADD approaches that support TCM research on COVID-19 have been reviewed in this paper. After determining hit selection, every study requires further experimental validations in order to be readily tested in animal and clinical studies.

Conclusion

Overall, different approaches supporting TCM research on COVID-19 including research databases, docking tools, and MD simulation software have been totally summarized. The application of databases and research resources on TCM ingredients for COVID-19 listed in this paper facilitates a wide range of audience to employ CADD tools to datasets and biological targets regarding to SARS-CoV-2 drug discovery. Computational investigation including databases, molecular docking tools and MD simulation software on natural compounds and TCM herbs have been applied and predicted as potential targets for COVID-19. The most commonly used database, molecular docking tool, and MD simulation software include TCMSP, AutoDock Vina, and GROMACS respectively. These are subsequently illustrated in Figure 2, 4, and 5 as pie charts. MD simulation software is implemented for MM/PBSA and MM/GBSA methods for

binding free energy calculation. Several examples of active components derived from TCM by structure-based and ligand-based approaches were also mentioned, which were conducted *in vitro* and *in silico* respectively. Active components derived from natural products or TCM for structure-based approaches are summarized against key COVID-19 targets including ACE2, $3CL^{pro}$, and PL^{pro}. Only few studies were found in active ingredients of natural products derived from TCM for ligand-based approaches. COVID-19 knowledge graph, an example of knowledge mining tool, is used to analyze complex TCM relationships between TCM herbal properties and therapeutics on COVID-19 infected patients. System/network pharmacology databases were used to identify the multitarget mechanisms of COVID-19 due to the complex of chemical ingredients, targets, and pathological mechanisms in multiple TCM herbs. In the future, computational approaches, tools, and resources are necessary for the upcoming unknown diseases. We recommend readers to exploit our information for the development of future drug discovery in TCM.

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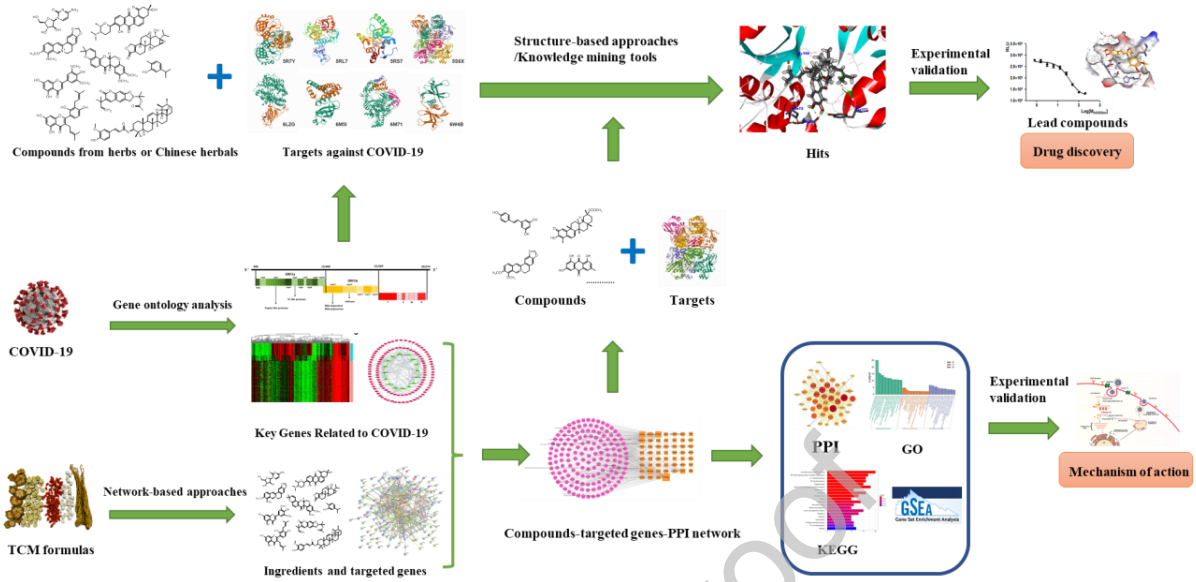


Figure 1 General Procedure of Computational Approaches.

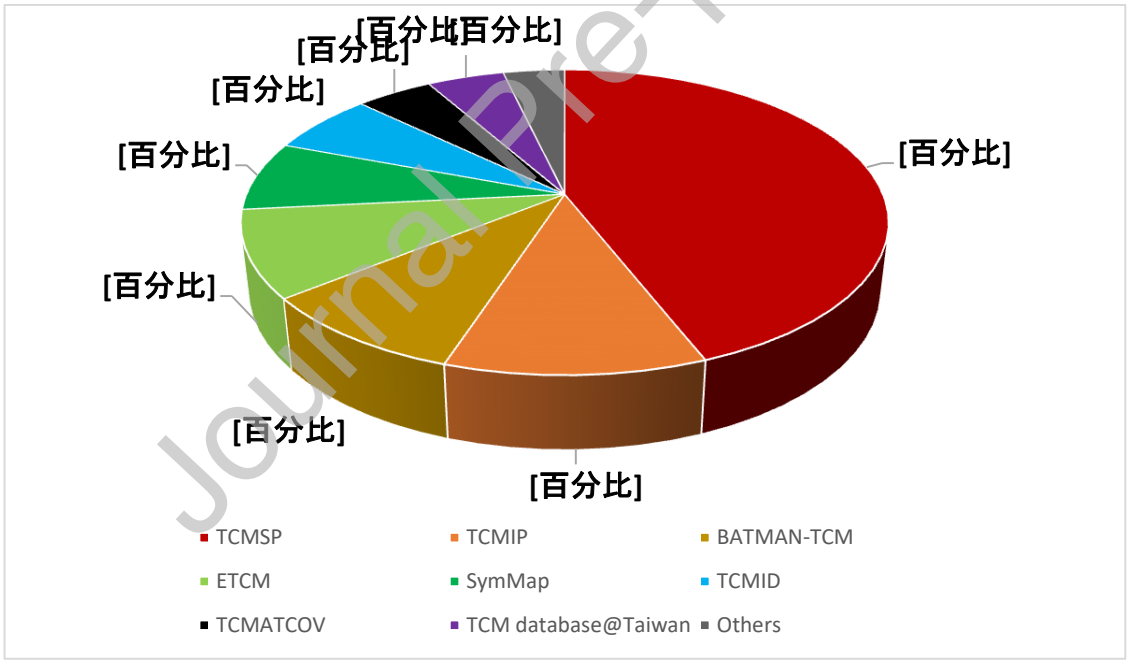


Figure 2 Databases Supporting TCM Research against COVID-19.

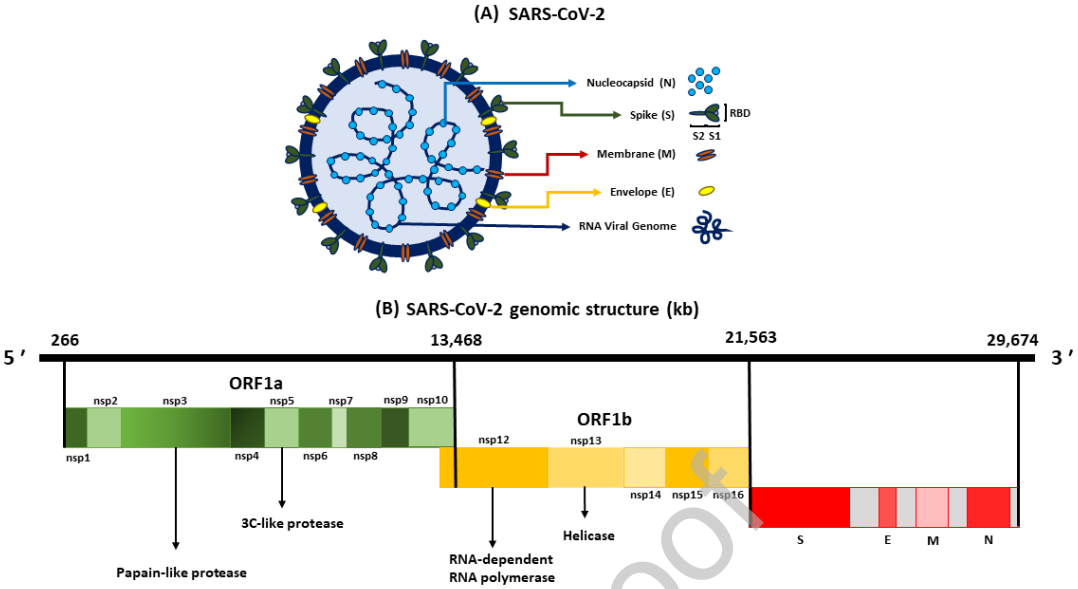


Figure 3 Structure of SARS-CoV-2. (A) Schematic representation of the structure of SARS-CoV-2. It has four structural proteins, S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins; the N protein holds the single strand, positive-sense RNA genome, and the S, E, and M proteins together create the viral envelope. (B) SARS-CoV-2 genomic structure.

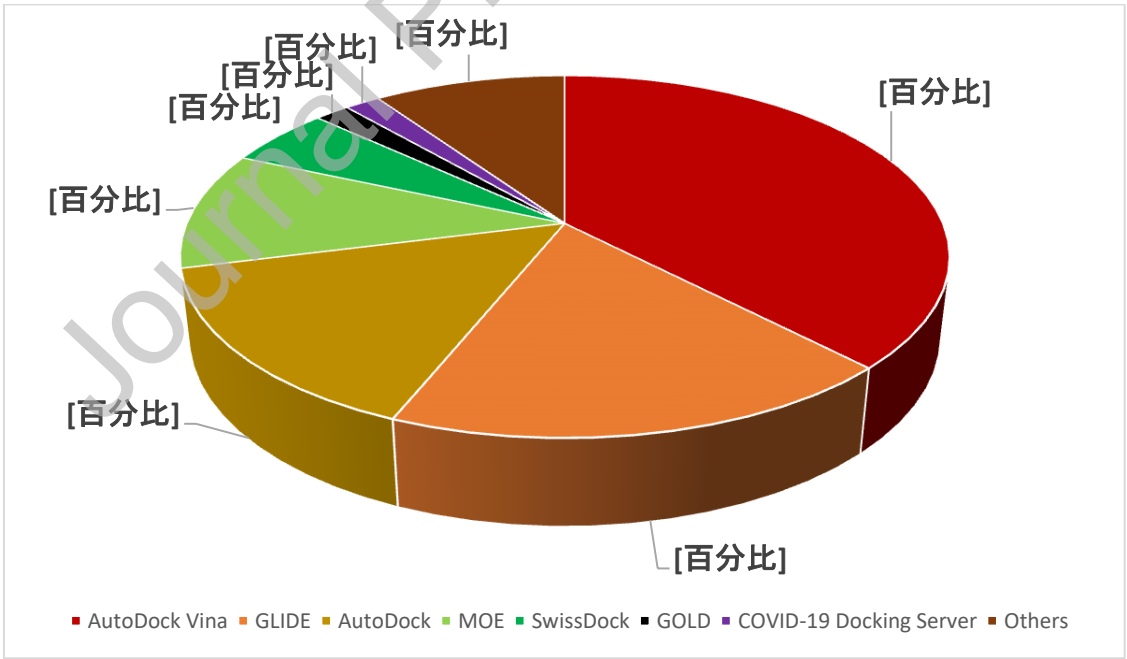


Figure 4 Docking Tools Supporting TCM Research against COVID-19.

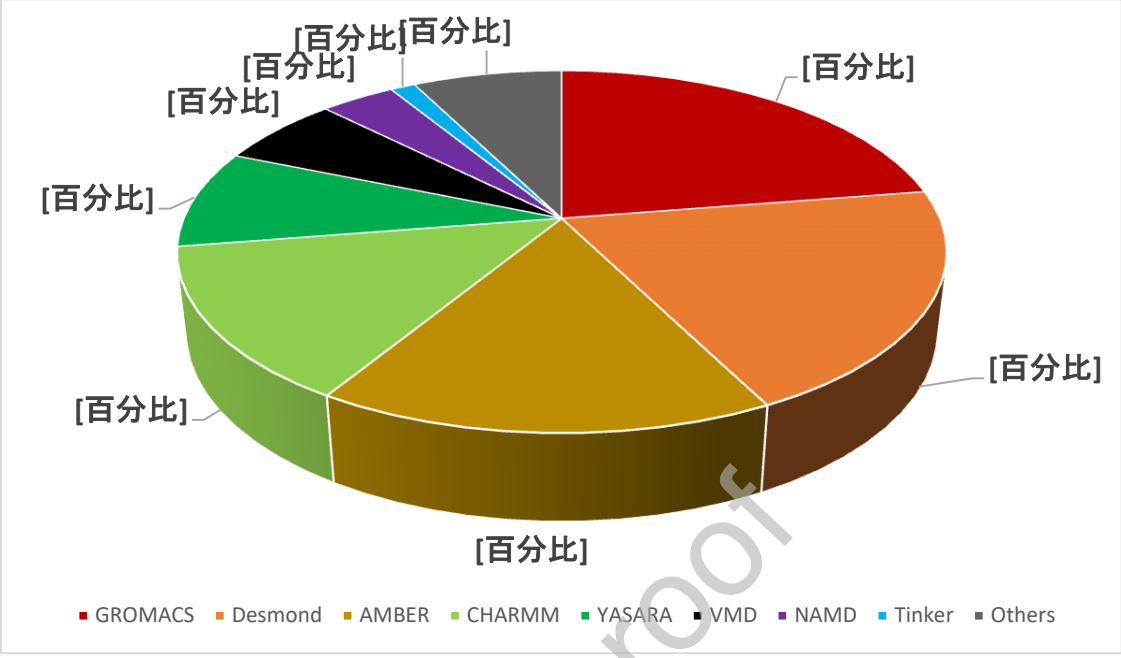


Figure 5 MD Simulation Software Supporting TCM Research against COVID-19.

Table 1 Docking tools that support research of TCM against COVID-19

Docking tools	Website	Description	License	References
AutoDock	https://autodock.scripps.edu/	Automated docking tools for predicting the binding between substrates (ligand) and a known 3D structural receptor (protein)	Free	(Abd El-Mageed et al., 2021; Gentile et al., 2020; Huang et al., 2021; Li et al., 2021a; Mazzini et al., 2020; Morris et al., 2008; Mu et al., 2021; Niu et al., 2021; Prasanth et al., 2021; Saidijam et al., 2021; Sivaraman and Pradeep, 2020; Vardhan and Sahoo, 2021; Wang et al., 2021c; Xia et al., 2020; Xiong et al., 2020; Yu et al., 2020; Zhang et al., 2020; Zhao et al., 2020b)
AutoDock Vina	https://vina.scripps.edu/	An open-source program with more accurate binding mode of predictions compared to AutoDock	Free	(Alhadrami et al., 2021; Arora et al., 2020; Beirami et al.; Bharadwaj et al., 2020; Bung et al., 2021; Gao et al., 2020; Gentile et al., 2020; Gu et al., 2021; Guo et al., 2020; Hasan et al., 2022; Huynh et al., 2020; Khuntia et al., 2021; Li et al., 2021a; Liao et al., 2021; Liu et al., 2021a; Mazzini et al., 2020; Mu et al., 2021; Murugan et al., 2021; Peng et al., 2020;

				Prasanth et al., 2021; Rajpoot et al., 2021; Ram et al., 2021; Ruan et al., 2020; Shree et al., 2022; Simayi et al., 2022; Singh et al., 2020; Sinha et al., 2021a; Sinha et al., 2020; Trott and Olson, 2010; Vardhan and Sahoo, 2021; Wang et al., 2021d; Wei et al., 2020; Wu et al., 2021a; Wu et al., 2021b; Xia et al., 2020; Xie et al., 2021b; Xu et al., 2021b; Ye et al., 2020; Ye et al., 2021; Yu and Li, 2022; Zackria et al., 2021; Zhang et al., 2020; Zhao et al., 2020b; Zhao et al., 2021c; Zheng et al., 2020)
COVID-19 Docking Server	https://ncov.schanglab.org.cn/	A web server for predicting the interaction between small molecules, peptides and antibodies and COVID-19 protein targets	Free	(Cai et al., 2021; Chen et al., 2020; Kong et al., 2020b)
GLIDE	https://www.schrodinger.com/products/glide	A ligand-receptor docking program from HTVS to SP to XP at high accuracy levels	Commercial	(Chen et al., 2021b; Chikhale et al., 2020a; Chikhale et al., 2020b; Dutta et al., 2021; Emirik, 2020; Fathy et al., 2020; Kumar et al., 2020; Li et al., 2021b; Liao et al., 2021; Liu et al., 2021b; Mahmud et al., 2021; Mei et al., 2021; Rajan et

				al., 2020; Rakib et al., 2020; Repasky et al., 2007; Selvaraj et al., 2021a; Selvaraj et al., 2021b; Shah et al., 2021; Shawky et al., 2020; Shree et al., 2022; Sinha et al., 2021b; Zhao et al., 2021a)
GOLD	https://www.ccdc.cam.ac.uk/solutions/csd-discovery/Components/Gold/	A protein-ligand docking software with optimized scoring functions for drug discovery	Commercial	(Nawrot-Hadzik et al., 2021; Tejera et al., 2022; Verdonk et al., 2003)
MOE	https://www.chemcomp.com/Products.htm	A comprehensive package for visualizing, modeling, and simulating computer aided molecular design of small molecules, peptides, and biologics	Commercial	(Chikhale et al., 2020a; Elebeedy et al., 2021; Han et al., 2020; Liao et al., 2021; Rauf et al., 2021; Saidijam et al., 2021; Tahir Ul Qamar et al., 2020; Vilar et al., 2008; Wang et al., 2020; Wei et al., 2020; Yu et al., 2021; Zaki et al., 2021)
SwissDock	http://www.swissdock.ch/	A web server for predicting the interaction between a target protein and small molecule	Free	(Arora et al., 2020; Chen et al., 2021a; Grosdidier et al., 2011; Kong et al., 2020a; Lung et al., 2020; Rajpoot et al., 2021; Zhang et al., 2021b)

Table 2 MD simulation software that support research of TCM against COVID-19

Docking tools	Website	Description	License	Reference
AMBER	https://ambermd.org/	A package of biomolecular simulation software including MM force fields and MD simulations	Free	(Case et al., 2005; Chikhale et al., 2020a; Chikhale et al., 2020b; Dutta et al., 2021; Gentile et al., 2020; Gopinath et al., 2020; Liao et al., 2021; Liu et al., 2021a; Murugan et al., 2021; Shree et al., 2022; Wang et al., 2021b; Wang et al., 2020; Wei et al., 2020; Ye et al., 2020)
YASARA	http://yasara.org/	A molecular-graphics, modeling, and simulation program for visualizing bioinformatics	Proprietary	(Dutta et al., 2021; Gentile et al., 2020; Land and Humble, 2018; Mahmud et al., 2021; Patel et al., 2021; Shree et al., 2022; Swargiary et al., 2020; Xinqiang et al., 2020)
GROMACS	http://www.gromacs.org/	An MD package for complex bonded interactions including proteins, lipids, and nucleic acids, as well as polymers	Free	(Abraham et al., 2015; Chen et al., 2021a; Elekofehinti et al., 2021; Khuntia et al., 2021; Mazzini et al., 2020; Prasanth et al., 2021; Rajpoot et al., 2021; Selvaraj et al., 2021b; Sinha et al., 2020; ul Qamar et al., 2020; Vardhan and Sahoo, 2021; Wu et al., 2021b; Xie et al., 2021a; Xie et al., 2021b; Ye et al., 2020; Zackria et al., 2021; Zaki et al., 2021; Zhao et al., 2021c)
VMD	http://www.ks.uiuc.edu/Research/vmd/	A molecular visualization program supporting large biomolecular systems using 3-D graphics and built-in scripting	Proprietary and free	(Abd El-Mageed et al., 2021; Alhadrami et al., 2021; Humphrey et al., 1996; Khuntia et al., 2021; Vardhan and Sahoo, 2021; Zaki et al., 2021)
NAMD	http://www.ks.uiuc.edu/Research/namd/	A parallel MD code designed for high-performance simulation of large biomolecular systems using the setup and trajectory analysis of VMD program	Proprietary and free	(Abd El-Mageed et al., 2021; Alhadrami et al., 2021; Huynh et al., 2020; Phillips et al., 2005)
CHARMM	https://www.charmm.org/	A biomolecular simulation program with comprehensive set of energy functions, various enhanced sampling approaches as well as multi-scale techniques	Proprietary and commercial	(Abd El-Mageed et al., 2021; Alhadrami et al., 2021; Arora et al., 2020; Brooks et al., 2009; Chen et al., 2021a; Huynh et al., 2020; Khuntia et al., 2021; Mazzini et al., 2020; Ram et al., 2021; Sinha et al., 2020; Zaki et al., 2021; Zhao et al., 2021c)
Desmond	https://www.deshawresearch.com/resources.html	A high-speed MD software suite on biological system with high performance and accuracy on NVIDIA GPUs	Proprietary and commercial	(Abel et al., 2020; Alhadrami et al., 2021; Badraoui et al., 2022; Bharadwaj et al., 2020; Emirik, 2020; Gopinath et al., 2020; Hasan et al., 2022; Kumar et al., 2020; Li et al., 2021b; Patel et al., 2021; Ram et al., 2021; Shah et al., 2021; Shree et al., 2022; Şimşek et al., 2021; Singh et

				al., 2020; Vetrivel et al., 2021)
Tinker	https://dasher.wustl.edu/tinker/	A molecular modeling program for MM and MD including several commonly used parameters for molecular design	Proprietary	(Mazzini et al., 2020; Rackers et al., 2018)

Table 3 Examples of active compounds isolated from natural extracts with ACE2 (S protein) inhibitory activity

Source	Family	Hits	Class of compounds	Bioactivities	References
Camellia sinensis (Linnaeus) Kuntze	Theaceae	Epigallocatechin gallate (EGCG)	Catechin	IC_{50} = 2.47 μg/mL	(Henss et al., 2021)
Caragana sinica (Buc'hoz) Rehder	Fabaceae	Kobophenol A	Stilbenoid	IC_{50} = 1.81 μM EC_{50} = 71.6 μM	(Gangadevi et al., 2021)
Glycyrrhiza glabra Linnaeus	Fabaceae	Glycyrrhizic acid	Triterpenes	IC_{50} = 22 μM	(Yu et al., 2021)
Polygonum cuspidatum (Houttuyn) Ronse Decraene	Polygonaceae	Emodin 8-*O*-β-D-glucoside	Hydroxyanthraquinone glycoside	IC_{50} = 22.50 μmol/L	(Chen et al., 2021b)
Rheum palmatum Linnaeus	Polygonaceae	Rhein	Anthraquinone	IC_{50} = 18.33 μmol/L	
Salvia miltiorrhiza Bunge	Lamiaceae	Tanshinone IIA,	Diterpene quinone	IC_{50} = 4.08 μM	(Elebeedy et al., 2021)
		Carnosic acid	Phenolic acids	IC_{50} = 15.37 μM	
		Rosmarinic acid	Diterpene	IC_{50} = 25.47 μM	
		Salvianolic acid B	Polyphenols	IC_{50} = 58.29 μM EC_{50} = 6.22 μM	(Elebeedy et al., 2021) (Hu et al., 2021b)
		Salvianolic acid C		EC_{50} = 10.14 μM	(Hu et al., 2021b)
		Salvianolic acid A		EC_{50} = 11.31 μM	

Table 4 Examples of active compounds isolated from natural extracts with $3CL^{pro}$ (M^{pro}) inhibitory activity

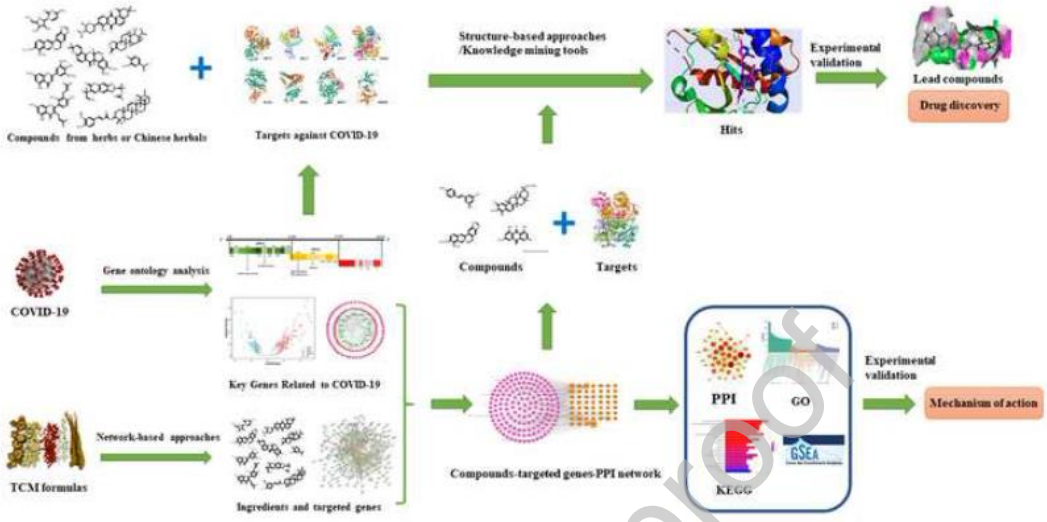
Source	Family	Hits	Class of compounds	Bioactivities	References
Actinomycetes QFPD	Actinomycetaceae	Leupeptin	Tripeptide	IC_{50} = 127.2 μM EC_{50} = 42.34 μM	(Fu et al., 2021)
Aloe vera (Linnaeus) Burman	Asphodelaceae	Kaempferol	Flavonoid	93% inhibition at 62.5 μM 88% inhibition at 125 μM	(Khan et al., 2021)
Ampelopsis japonica (Thunberg) Makino	Vitaceae	Myricetin	Flavonoid	IC_{50} = 2.86 μM IC_{50} = 3.684 μM	(Xiao et al., 2021)
Anacardium occidentale Linnaeus	Anacardiaceae	Anacardic acid	Phenolic acid	IC_{50} = 2.07 μM	(Chen et al., 2021c)
Camellia sinensis (Linnaeus) Kuntze	Theaceae	Epigallocatechin gallate (EGCG)	Catechin	IC_{50} = 0.874 μM	(Du et al., 2021)
Cannabis sativa Linnaeus	Cannabaceae	Cannabidiol	Cannabinoid	IC_{50} = 7.91 μM	(Raj et al., 2021)
		Δ^9 - tetrahydrocannabinol		IC_{50} = 10.25 μM	
Cirsium japonicum de Candolle	Asteraceae	Pectolinarin	Flavonoid	IC_{50} = 37.78 μM	(Jo et al., 2020)
Ginkgo biloba Linnaeus	Ginkgoaceae	Ginkgolic acid	Phenolic acid	IC_{50} = 1.79 μM	(Chen et al., 2021c)
Linum usitatissimum Linnaeus	Linaceae	Herbacetin	Flavonoid	IC_{50} = 33.17 μM	(Liu et al., 2021b)
Poria cocos (F.A. Wolf) Ryvarden & Gilbertson	Polyporaceae	Pachymic acid	Triterpenoid	IC_{50} = 18.607 μmol/L	(Wu et al., 2021b)
Rhus succedanea (Linnaeus) Kuntze	Anacardiaceae	Rhoifolin	Flavonoid	IC_{50} = 27.45 μM	(Liu et al., 2021b)
Scutellaria baicalensis Georgi	Lamiaceae	Baicalin	Flavone glycoside	IC_{50} = 6.41 μM	(Su et al., 2020)
		Baicalein	Flavone	IC_{50} = 0.94 μM	
				IC_{50} = 0.39 μM EC_{50} = 2.9 μM	(Liu et al., 2021b)
		Scrutellarein	Flavonoid	IC_{50} = 5.8 μM	

Table 5 Examples of active compounds isolated from natural extracts with PL^{pro} inhibitory activity

Source	Family	Hits	Class of compounds	Bioactivities	Reference
Carpobrotus edulis (Linnaeus) Brown	Aizoaceae	Rutin	Flavonol glycoside	38% inhibition at 100 μM	(Pitsillou et al., 2021)
Garcinia lateriflora Blume	Clusiaceae	Morelloflavone		IC_{50} = 36.4 μM	(Li et al., 2022b)
Ginkgo biloba Linnaeus	Ginkgoaceae	Amentoflavone	Biflavones	IC_{50} = 13.0 μM	
		Ginkgetin		IC_{50} = 29.8 μM	
		Isoginkgetin		IC_{50} = 31.2 μM	
		Sciadopitysin		IC_{50} = 34.8 μM	
Hibiscus sabdariffa Linnaeus	Malvaceae	Cyanidin-3-O-glucoside	Anthocyanin	20% inhibition at 100 μM	(Pitsillou et al., 2021)
Hypericum perforatum Linnaeus	Hypericaceae	Hypericin	Naphtodianthrone	97% inhibition at 100 μM	
Lonicera japonica Thunberg	Caprifoliaceae	4'-O-Methylochnaflavone		IC_{50} = 22.8 μM	(Li et al., 2022b)
Platycladus orientalis (Linnaeus) Franco	Cupressaceae	Hinokiflavone		IC_{50} = 9.5 μM	
		Cryptomerin B		IC_{50} = 26.3 μM	
Podocarpus nakaii Hayata	Podocarpaceae	Podocarpusglavone		IC_{50} = 43.2 μM	
Salvia miltiorrhiza Bunge	Lamiaceae	Cryptotanshinone	Diterpenoid	IC_{50} = 5.63 μmol/L	(Zhao et al., 2021b)
		Tanshinone I		IC_{50} = 2.21 μmol/L	

Abbreviations

TCM: Traditional Chinese medicine
DAAs: Direct-acting antiviral agents
CADD: Computer-aided drug design
AI: Artificial Intelligence
MD: Molecular dynamic
ML: Machine learning
MOA: Mechanism of action
ADMET: Absorption, distribution, metabolism, excretion, and toxicity
QSAR: Quantitative structure–activity relationship
DEGs: Differentially expressed genes
HTVS: High Throughput virtual screening
SP: Standard Precision
XP: Extra Precision
SBDD: Structure-based drug discovery
MM/PBSA: Molecular Mechanics Poisson-Boltzmann Surface area
MM/GBSA: Molecular Mechanics Generalized Born Surface area
QM: Quantum mechanics
DFT: Density Functional Theory
GO: Gene Ontology
KEGG: Kyoto Encyclopedia of Genes and Genomes
SFJDC: Shufeng Jiedu Capsule
PPI: Protein-protein interaction
ANNs: Artificial Neural Networks
MXSGD: Maxing Shigan Decoction
TJQWG: Toujie Quwen Granules
HSBDF: Huashi Baidu Formula
LHQWC: Lianhua Qingwen Capsule
SLBZS: Shenling Baizhu San
QFPDT: Qingfei Paidu Tang
ZQF: Zhongqi Fangzi
GZTCJ: Guizhi Tang Chongji
SFZSY: Shenfu Zhusheye
HSYFF: Hanshiyufen Fang
XCT: Xiangchuan Tang
SQRSS: Shunqi Renshen San
CCJ: Chaichen Jian
XFBDF: Xuanfei Baidu Fang
SFHF: Shenfuhuang Formula
SPR: Surface plasmon resonance
HPLC: High-performance liquid chromatography
HRMS: High-resolution mass spectrometry
FRET: Fluorescence resonance energy transfer
Generative Topographic Mapping (GTM)
DL: Deep learning
NCEs: New chemical entities
CNNs: Convolutional Neural Networks
KG: Knowledge graph
OB: Oral bioavailability
DL: Drug likeness



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